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PATENT & TRADEMARK OFFICE

APPL. NO.	:	09/357,349
APPLICANTS	:	Geerts, *et al.*
FILED	:	July 14, 1999
TITLE	:	Neurotrophic Growth Factor
TC/AU	:	1647
EXAMINER	:	Sharon L. Turner, Ph.D.
DOCKET NO	:	43962–010700

REQUEST FOR INTERFERENCE PURSUANT TO 37 C.F.R. § 41.202

Sir:

The instant Request for Interference is being filed concurrently with a Response to the Notice of Non-Compliant Amendment in the above-identified Application.

No fee is deemed necessary in connection with the filing of this Request. However, if any fee is required, authorization is hereby given to charge of amount of such fee to Greenberg Traurig, LLP Deposit Account No. 50-1561.

(1) Identification of the Patent under 37 C.F.R. § 41.202(a)(1)

Pursuant to 37 C.F.R. § 41.202(a)(1), Applicants request the declaration of an Interference between the above-identified Application and United States Patent No. 6,734,284, issued May 11, 2004, issued to Teit E. Johansen, *et al.* (hereinafter "the Johansen Patent"). A copy of the Johansen Patent is attached hereto as **Exhibit A**. The Johansen Patent purports on its face to be assigned to NsGene A/S, Ballerup (DK).

(2) Proposed Count and Identification of the Claims Corresponding to the Count under 37 C.F.R. § 41.202(a)(2)

Proposed Count 1 is directed to an isolated human neurotrophic-polypeptide, the polypeptide including an open reading frame having the amino acid sequence set forth below, and functional equivalent derivatives thereof. The following count is proposed:

Count 1:

An isolated polypeptide with neurotrophic activity, said polypeptide comprising an amino acid sequence:

AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLS
LASLLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG,

or a functional equivalent or a derivative thereof having at least 90% identity to said amino acid sequence.

Claims of the Johansen Patent Correspond to the Count:

Applicants respectfully submit that all nine claims in the Johansen Patent correspond to proposed Count 1.

Claim 1 of the Johansen Patent corresponds to the proposed Count 1. Claim 1 is directed to an isolated neublastin polypeptide with neurotrophic activity, having certain physical characteristics with respect to SEQ ID NO:2. In Table 1, a Clustal W alignment is provided, showing SEQ ID NO:2 from the Johansen Patent (a/k/a Neublastin), aligned to the polypeptide sequence of the proposed Count 1. Numbering of SEQ ID NO:2 in accordance with the scheme given in the Johansen Patent begins at the N-terminal serine as residue 1, and does not include the five deleted residues, (*i.e.,* the glycine residues downstream of the gap are numbered 4 and 5), consistent with the numeration of SEQ ID NO:2 in the Johansen Patent.

TABLE 1.

CLUSTAL W (1.82) Multiple Sequence Alignment of Neublastin (SEQ ID NO:2) to Proposed Count 1.

```
Neublastin      ---SGS-----GGAGCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLAS 52
Count 1         AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
                    **      *  **************************** *** ************

Neublastin        LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 105
Count 1           LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
                  ******************************************************
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SEQ ID NO:2, when numbered in as recited in the Johansen Patent, has the following structural properties:

(a) seven conserved cysteine residues at positions 8, 35, 39, 72, 73, 101, and 103;

(b) amino acid residues as follows:
C at position 8, L at position 10, V at position 17, L at position 20, G at position 21, L at position 22, G at position 23, E at position 28, F at position 32, R at position 33, F at position 34, C at position 35, G at position 37, C at position 39, C at position 72, C at position 73, R at position 74, P at position 75, F at position 83, D at position 85, S at position 97, A at position 98, C at position 101 and C at position 103; and

(c) an LGLG repeat, an FRFC motif, a QPCCRP motif, and a SATACGC motif.

As can be seen in Table 1, the sequence provided in the proposed Count 1, if numbered in accordance with SEQ ID NO:2 (*i.e.,* not counting the 8 additional amino acids at the N-terminus), would have the identical structural properties and numeration recited in claim 1.

Claim 1 also provides that the isolated neublastin polypeptide has neurotrophic activity, which corresponds to the neurotrophic activity recited by the proposed Count 1. Claim 1 also encompasses sequences having at least 90% sequence identity to the sequence set forth in proposed Count 1. As seen in Table 1, the sequence of the proposed Count differs by only 5 amino acids compared to the sequence of amino acids 1-105 recited by claim 1, resulting in greater than 95% identity between the two.

Claims 2-7 of the Johansen Patent are all directed to isolated polypeptides with neurotrophic activity, all having amino acid sequences that fall within the scope of claim 1. Since claims 2-7 are all directly or indirectly dependent on claim 1 and the proposed count corresponds to claim 1 of the Johansen Patent, then the polypeptides covered by claims 2-7 would all fall within the scope of independent claim 1, and accordingly, claims 2-7 all correspond to the proposed count.

Claim 8 of the Johansen Patent is drawn to glycosylated polypeptides of claims 1-7. The advantages of glycosylating neurotrophic polypeptides were well known at the time of filing of the Johansen Patent. For example, see, WO 97/08196 to Johnson *et al.,* published March 6,

1997, which discloses the neurotrophic growth factor neurturin, (shown in the Johansen Patent aligned with SEQ ID NO:2), in which WO 97/08196 discloses the mature neurotrophic growth factor neurturin is glycosylated. See also, Kotzbauer PT, *et al.,* (1996), Neurturin, a relative of glial-cell-line-derived neurotrophic factor. Nature. Dec 5;384(6608):467-70, which teaches the same. Likewise see, Lin LF, (1994) Purification and initial characterization of rat B49 glial cell line-derived neurotrophic factor. J. Neurochem. Aug; 63(2):758-68, which teaches that human glial cell line-derived neurotrophic factor (GDNF), is heterogeneously glycosylated, and is a potent neurotrophic factor that exhibits relative specificity for the dopaminergic neurons, and promotes the survival, morphological differentiation, and high-affinity dopamine reuptake of dopaminergic neurons in midbrain cultures, without obvious effects on total neurons or glia and without increasing high-affinity GABA or serotonin reuptake. As before, the Johansen Patent provides an alignment of GDNF with SEQ ID NO:2. Therefore, the Patentee was aware that protein in this GDNF family are glycosylated, and it would have been an obvious variation of the invention to claim a glycosylated neublastin.

Claim 9 of the Johansen Patent is drawn to pharmaceutical compositions of the polypeptides of claims 1-8. The advantages of adding a pharmaceutical carrier to a polypeptide were well known at the time of filing of the Johansen Patent. See, Remington's Pharmaceutical Sciences, 19th Ed., Easton, Pa., Mack Publishing Co., 1995. Therefore a pharmaceutical preparation of neublastin would have been an obvious variation of the invention at the time of filing.

Accordingly, given that broad general knowledge of both glycosylation of neurotrophic factors (and peptides in general) as well as the incorporation of therapeutic peptides with pharmaceutical carriers, available in the art at the filing date of the Johansen Patent, claims 8 and 9 would have been obvious in light of polypeptide sequences in the proposed Count in view of the general knowledge on peptide glycosylation and pharmaceutical carriers known in the art.

Claims of the Instant Patent Application Correspond to the Count:

Proposed Count 1 is essentially identical to pending claim 7, as amended in the November 17, 2004 Amendment and Response. SEQ ID NO:3 is identical to the polypeptide sequence recited in the proposed Count 1. Applicants respectfully submit that all pending claims in the above-referenced Application (claims 7-9, as amended in the November 17, 2004 Amendment and Response) correspond to proposed Count 1. Claims 8-9 of the instant

Application further define the functional variant or derivative of polypeptides with neurotrophic activity comprising SEQ ID NO:3. Accordingly, claims 8-9 also correspond to proposed Count 1, which encompasses functional variant or derivative of these neurotrophic polypeptides.

(3) Claim chart of claims Corresponding to the Count under 37 C.F.R. § 41.202(a)(3)

As required under 37 C.F.R. § 41.202(a)(3), a claim chart is provided below to compare at least one claim of the Johansen Patent with at least one claim of the instant Application that correspond to proposed Count 1.

CLAIMS FROM THE JOHANSEN PATENT	CLAIMS FROM THE INSTANT APPLICATION
Claim 1. An isolated neublastin polypeptide with neurotrophic activity comprising the following:	**Claim 7.** An isolated human neurotrophic polypeptide, said polypeptide comprising
(a) seven conserved cysteine residues at positions 8, 35, 39, 72, 73, 101, and 103 when numbered in accordance with SEQ ID NO. 2; (b) amino acid residues as follows: C at position 8, L at position 10, V at position 17, L at position 20, G at position 21, L at position 22, G at position 23, E at position 28, F at position 32, R at position 33, F at position 34, C at position 35, G at position 37, C at position 39, C at position 72, C at position 73, R at position 74, P at position 75, F at position 83, D at position 85, S at position 97, A at position 98, C at position 101 and C at position 103, each when numbered in accordance with SEQ ID NO. 2; (c) an LGLG repeat, an FRFC motif, a QPCCRP motif, and a SATACGC motif; and	the amino acid sequence of SEQ ID NO:3,
(d) an amino acid sequence comprising at least 90% sequence identity to AA_1-AA_{105} of SEQ ID NO. 2.	or a functional equivalent or a derivative thereof. **Claim 8.** The isolated neurotrophic polypeptide of claim 7, wherein the derivative has at least 90% homology to SEQ ID NO:3. **Claim 9.** The isolated neurotrophic polypeptide of claim 8, wherein the derivative is SEQ ID NO:9 or SEQ ID NO:10.

For comparison purposes, a Clustal W sequence alignment of SEQ ID NO:2 in the claims of the Johansen Patent (designated as Neublastin by the Patentee) and SEQ ID NO:3 in claim 7 of the instant Application (designated as Enovin by the Applicant) is provided below in

Table 2. Conserved residues are indicated by a "*".

TABLE 2.

CLUSTAL W (1.82) Multiple Sequence Alignment of Neublastin (SEQ ID NO:2) to Enovin (SEQ ID NO:3)

```
Neublastin    ---SGS-----GGAGCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLAS 52
Enovin        AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
                  **      *  ***************************** *** ************

Neublastin      LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 105
Enovin          LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
                ******************************************************
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As can be seen by the sequence alignment above, SEQ ID NO:3 of the instant Application, when numbered in accordance with SED ID NO:2 in claim 1 of the Johansen Patent, also has (a) seven conserved cysteine residues, which correspond to those found at positions 8, 35, 39, 72, 73, 101, and 103 of SEQ ID NO:2 of the Johansen Patent; (b) corresponding amino acids to the C at position 8, L at position 10, V at position 17, L at position 20, G at position 21, L at position 22, G at position 23, E at position 28, F at position 32, R at position 33, F at position 34, C at position 35, G at position 37, C at position 39, C at position 72, C at position 73, R at position 74, P at position 75, F at position 83, D at position 85, S at position 97, A at position 98, C at position 101 and C at position 103, of SEQ ID NO:2 of the Johansen Patent; and (c) an LGLG repeat, an FRFC motif, a QPCCRP motif, and a SATACGC motif. Furthermore, SEQ ID NO:3 of the instant Application has 100 amino acids identical to AA_1-AA_{105} of the open reading frame of SEQ ID NO:2 of the Johansen Patent, representing greater than 90% identity (95.2%), as recited in element (d) of claim 1 of the Johansen Patent and in the proposed Count 1.

Accordingly, claim 7 of the instant Application, which is drawn to an isolated neurotrophic polypeptide comprising the amino acid sequence of SEQ ID NO:3 would have anticipated claim 1 of the Johansen Patent since SEQ ID NO:3 has the seven conserved cysteine residues of element (a), the corresponding amino acids of element (b), the repeat and motifs of element (c) of the Johansen Patent, and greater than 90% identity (95.2%) with SEQ ID NO:2 of the Johansen Patent.

Claim 8 of the instant Application (as amended in the November 17, 2004 Amendment and Response) further defines the functional equivalents or derivatives as having at least 90% homology to SEQ ID NO:3, a similar requirement to element (d) of claim 1 of the Johansen Patent. Claim 9 of the instant Application (as amended in the November 17, 2004 Amendment and Response) further defines the functional equivalents or derivatives as SEQ ID NO:9 or SEQ ID NO:10. As shown in Table 3, both of these sequences have the seven conserved cysteine residues of element (a), the corresponding amino acids of element (b), the repeat and motifs of element (c) of the Johansen Patent, and greater than 90% identity with SEQ ID NO:2 of the Johansen Patent. Accordingly, both claims 8 and 9 of the instant Application would have anticipated claim 1 of the Johansen Patent.

TABLE 3.

CLUSTAL W (1.82) Multiple Sequence Alignment of Neublastin (SEQ ID NO:2) to Enovin (SEQ ID NO:9)

```
Neublastin      ---SGS-----GGAGCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLAS 52
Enovin          AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
                    **      *  ***************************** *** ************

Neublastin        LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 105
Enovin            LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
                  ******************************************************
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CLUSTAL W (1.82) Multiple Sequence Alignment of Neublastin (SEQ ID NO:2) to Enovin (SEQ ID NO:10)

```
Neublastin      ---SGS-----GGAGCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLAS 52
Enovin          AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
                    **      *  ***************************** *** ************

Neublastin        LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 105
Enovin            LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
                  ******************************************************
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The Johansen Patent 6,734,284, is a divisional application claiming priority to USSN 09/347,613, which issued as US Patent 6,593,133. US Patent 6,593,133 is cited in the May 5, 2004 Office Action as anticipating claims 7-9 of the instant Application. As stated in the May 5, 2004 Office Action in the instant Application, "As noted in Johansen the peptide comprises a Pro domain which is cleaved to the mature form as disclosed in SEQ ID NO:12. Hence, instant

SEQ ID NO:3 ... is anticipated by Johansen SEQ ID NO:12." The Johansen SEQ ID NO:12 which has the seven conserved cysteine residues of element (a), the corresponding amino acids of element (b), the repeat and motifs of element (c) of the Johansen Patent, and greater than 90% identity (95.2%) with SEQ ID NO:2 and thus falls within the scope of claim 1 of the Johansen Patent. Accordingly, Claim 1 of the Johansen Patent encompasses the mature polypeptide of the Johansen SEQ ID NO:12 and claim 1 of the Johansen Patent would have thus anticipated claim 7 of the instant Application.

(4) Applicants Prevail on Priority

Applicants will prevail on priority, as required under 37 C.F.R. § 41.202(a)(4).

The Johansen Patent claims priority to four U.S. applications and three Danish applications: it is a divisional application of USSN 09/347,613 (now U.S. Pat. No. 6,593,133), filed Jul. 2, 1999, which claims the benefit of USSN 60/103,908, filed Oct. 13, 1998; DK 1998 01265, filed Oct. 6, 1998; USSN 60/097,774, filed Aug. 25, 1998; DK 1998 01048, filed Aug. 19, 1998; USSN 60/092,229, filed Jul. 9, 1998; and DK 1998 00904, filed July 6, 1998.

In the instant Application, Applicants claim the earliest priority to UK 9815283.8 filed July 14, 1998. The disclosure of the earliest priority application includes isolated polynucleotides encoding the functional Enovin mature polypeptide, immature polypeptide, and functional variants thereof.

In the November 17, 2004 Amendment and Response, Applicants filed a Declaration under 37 C.F.R. § 1.131, which has an attached Exhibit of a fax cover sheet and a portion of the enclosed draft disclosure materials for the patent Application. The disclosure materials disclosed the nucleic acid sequence encoding the functional Enovin mature polypeptide, the immature polypeptide, and functional variants thereof. Although the dates on the fax cover sheet were covered, the Declaration states that the fax was sent to Applicant's representative prior to July 6, 1998, thus establishing that Applicants were in possession of the claimed invention prior to July 6, 1998, the earliest apparent constructive reduction to practice of the Johansen patent. Applicants also attach hereto as **Exhibit B** a copy of an email correspondence between the inventor and a colleague disclosing the nucleic acid sequence and the amino acid sequence encoding the functional Enovin polypeptide. This email correspondence was sent on June 24, 1998, thus further establishing that Applicants were in possession of the claimed invention prior to July 6, 1998, the earliest apparent constructive

reduction to practice of the Johansen patent.

Moreover, although the earliest apparent constructive reduction to practice of the Johansen Patent is July 6, 1998, Applicants respectfully submit that the first actual constructive reduction to practice of the Johansen patent occurred much later. The polynucleotide and amino acid sequences provided in the earlier priority patent applications differed from Enovin in several ways, including but not limited to (i) lacking the 14 N-terminal amino acids; and (ii) including at least one structurally-significant point mutation (R158P). Thus, Applicants respectfully submit that the neublastin protein disclosed in the earlier priority applications was not Enovin and was not functionally equivalent to Enovin. The correct sequence was only introduced in later-filed priority applications. For example, the first presentation of a sequence without the structurally-significant point mutation (R158P) was in the patent application DK 1998 01048, filed Aug. 19, 1998. Accordingly, Applicants respectfully submit that Applicants' priority patent application (UK 9815283.8 filed July 14, 1998) discloses the correct sequence encoding the functional Enovin polypeptide and represents an earlier constructive reduction to practice than the first constructive reduction to practice of the Johansen Patent.

For the reasons discussed above, Applicants respectfully submit that the instant invention will prevail on priority.

(5) Support for Added or Amended Claims under 37 C.F.R. § 41.202(a)(5)

Pursuant to 37 C.F.R. § 41.202(a)(5), support for amended claims 7-9 of the instant Application is provided in the chart below.

AMENDED CLAIMS	SUPPORT IN DISCLOSURE FOR AMENDMENTS
Claim 7. An isolated human neurotrophic polypeptide,	Page 4, lines 31-end through page 5, lines 1-2; page 11, lines 14-20; page 14, lines, 1-8, and 15-31.
said polypeptide comprising the amino acid sequence of SEQ ID NO:3,	SEQ ID NO:3; FIG. 1.
or a functional equivalent derivative thereof.	Page 11, lines 14-20; FIG. 21; page 13, lines 2-11; page 29, lines 11-end through page 31, lines 1-18; FIG. 22; SEQ ID NO:9 and SEQ, ID NO:10.
Claim 8. The isolated neurotrophic polypeptide of claim 7, wherein the derivative has at least 90% homology to SEQ ID NO:3.	Page 13, lines 2-11

Claim 9. The isolated neurotrophic polypeptide of claim 8, wherein the derivative is SEQ ID NO:9 or SEQ ID NO:10.	Page 29, lines 11-end through page 31, lines 1-18; FIG. 22; SEQ ID NO:9 and SEQ ID NO:10.

(6) Support for Constructive Reduction to Practice under 37 C.F.R. § 41.202(a)(6)

Pursuant to 37 C.F.R. § 41.202(a)(6), support for each constructive reduction to practice is provided in the chart below.

AMENDED CLAIMS	SUPPORT IN DISCLOSURE FOR EACH RTP
Claim 7. An isolated human neurotrophic polypeptide,	**USSN 09/357,349**: Page 4, lines 27-end; FIG. 1. **USSN 09/327,668**: Page 4, lines 27-end; FIG. 1. **USSN 09/248,772:** Page 4, lines 27-end; FIG. 1. **UK 9815283.8**: Page 4, lines 15-23; FIG. 1.
said polypeptide comprising the amino acid sequence of SEQ ID NO:3,	**USSN 09/357,349**: Page 25, lines 18-end, through page 26, lines 1-2. **USSN 09/327,668**: Page 20, lines 24-end, through page 21, lines 1-6. **USSN 09/248,772**: Page 15, lines 9-26; FIG. 1. **UK 9815283.8**: Page 12, lines 14-21; FIG. 1.
or a functional equivalent derivative thereof.	**USSN 09/357,349**: Page 11, lines 14-end, through page 13, lines 1-2. **USSN 09/327,668**: Page 10, lines 16-end, through page 12, lines 1-9. **USSN 09/248,772**: Page 9, lines 14-end, through page 10, lines 1-32. **UK 9815283.8**: Page 8, lines 3-end, through page 9, lines 1-5.
Claim 8. The isolated neurotrophic polypeptide of claim 7, wherein the derivative has at least 90% homology to SEQ ID NO:3.	**USSN 09/357,349**: Page 13, lines 7-11. **USSN 09/327,668**: Page 12, lines 5-9. **USSN 09/248,772**: Page 10, lines 23-32. **UK 9815283.8**: Page 4, lines 31-end, through page 5 lines 1-13.

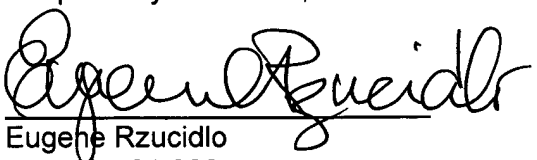
Applicants respectfully submit that the chart above clearly demonstrates that the instant Application and each of the priority applications provide a constructive reduction to practice within the scope of the interfering subject matter of proposed Count 1.

CONCLUSION

Applicants respectfully request that an interference be declared employing Count 1 with claims 1-9 of the Johansen Patent and claims 7-9 of the instant Application. Such action is respectfully requested.

Respectfully submitted,

Dated: March 1, 2005



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Unknown

From: Stefan Masure at JanBeBeCCM06[:]
Sent: Wednesday, June 24, 1998 6:35 AM
To: Jean-Marc Neefs at JnjBeBeCCM03
Subject: Nieuw homoloog

Jean-Marc,

Hieronder de (partiele) sequentie van het nieuwe homoloog (sequentie afgeleid van PCR product). Eerst de afgeleide AZ sequentie, dan de DNA sequentie.

Stefan

>PNH (direct) 140aa
PPQPSRPAPPPPAPPSALPRGGRAARAGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCS
GSCRRARSPHDLSLASLLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG*

>PNH_DNA (direct) 439bp

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CGCGGCGCGGGCTGGGGGCCCGGGCAGCCGCGCTCGGGCAGCGGGGGCGCGGGGCTGCCGCCTGCGCTC
G

CAGCTGGTGCCGGTGCGCGCGCTCGGCCTGGGCCACCGCTCCGACGAGCTGGTGCGTTTCCGCTTCTGCA

GCGGCTCCTGCCGCCGCGCGCGCTCTCCACACGACCTCAGCCTGGCCAGCCTACTGGGCGCCGGGGCCCT

GCGACCGCCCCCGGGCTCCCGGCCCGTCAGCCAGCCCTGCTGCCGACCCACGCGCTACGAAGCGGTCTCC
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GAGGGCTCGCTCCAGGGCT